

Fracture Incidence in Polyostotic Fibrous Dysplasia and the McCune-Albright Syndrome

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ABSTRACT: In patients with polyostotic fibrous dysplasia of bone, the peak incidence of fractures is during the first decade of life, followed by a decrease thereafter. Phosphaturia is associated with an earlier incidence and increased frequency of fractures.

Introduction: Fibrous dysplasia (FD) is a disorder involving either one (monostotic) or several bones (polyostotic FD [PFD]) and sometimes is associated with cafe-au-lait hyperpigmentation of the skin and one or more hyperfunctioning endocrinopathies (McCune-Albright syndrome [MAS]). Both PFD and MAS are often associated with phosphaturia. Although fractures occur frequently in PFD/MAS, fracture incidence and the effect of age and co-existing metabolic abnormalities (endocrinopathy and/or phosphaturia) on fractures are ill defined.

Materials and Methods: We reviewed the medical records and examined the endocrine and phosphorus metabolism of 35 patients with PFD/MAS. We report on the age at which extremity fractures occurred and their location and treatment. The results of endocrine and phosphorus metabolism testing and associations between age of first fractures, number of fractures, fracture rate, and metabolic abnormalities were noted.

Results: The average follow-up was 14.2 years (range, 2–39 years), during which 172 fractures occurred. The number and sites of fractures were 103 femoral, 25 tibial, 33 humeral, and 11 forearm. Twenty-seven patients had PFD with one or more endocrinopathies and/or phosphaturia, and eight had PFD alone. The endocrinopathies included precocious puberty ($n = 19$), hyperthyroidism ($n = 9$), growth hormone excess ($n = 6$), and one patient each with Cushing syndrome and primary hyperparathyroidism. Twelve patients had phosphaturia. The peak rate of fractures occurred between 6 and 10 years of age and decreased thereafter. Patients with metabolic abnormalities sustained their first fracture at an earlier age (6.9 versus 16.6 years, $p < 0.005$) and had a higher lifetime rate of fractures (0.29 versus 0.08 fractures/year, relative to patients with PFD alone. Phosphaturia was the single metabolic dysfunction associated with both an earlier age of first fracture (5.1 versus 16.6 years, $p < 0.05$) and a greater lifetime fracture rate (0.35 versus 0.08 fractures/year, $p < 0.05$).

Conclusions: The occurrence of extremity fractures in FD peaks between 6 and 10 years of age and declines thereafter. Fractures occur earlier and more frequently in the presence of phosphaturia. These data have implications for long-term prognosis, clinical management, and interpretation of therapeutic interventions.

J Bone Miner Res 2004;19:571–577. Published online on December 22, 2003; doi: 10.1359/JBMR.0301262

INTRODUCTION

FIBROUS DYSPLASIA (FD) is a skeletal disorder characterized by replacement of normal bone and marrow by benign fibro-osseous tissue.^(1–4) It can occur in one bone (monostotic) or several bones (polyostotic FD [PFD]). McCune-Albright syndrome (MAS) is classically defined by the triad of PFD, cafe-au-lait skin hyperpigmentation,

and hyperfunctioning endocrinopathies, and is often associated with phosphaturia.^(5–9) The accompanying endocrinopathies and phosphaturia may have a direct effect on the fibrous dysplastic skeleton,^(10–12) because it is known that hyperthyroidism and phosphaturia have deleterious effects on the normal skeleton.^(13,14)

The molecular basis of FD is postzygotic activating mutations of the *GNAS1* gene, which codes for the cyclic adenosine monophosphate (cAMP)-regulating α subunit ($G\alpha$) of the G-protein complex.^(15,16) When the mutation

The authors have no conflict of interest.

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occurs in bone, it results in accumulation of progenitor cells and deranged differentiation of these cells as they progress along the osteogenic pathway.⁽²⁾ This results in formation of abnormal bone and fibrotic tissue, which are composed of a mosaic of mutated and nonmutated osteogenic cells.⁽¹⁷⁾

The primary orthopedic problems associated with FD are pain, fracture, and deformity (one example is the pathognomonic shepherd's crook deformity of the proximal femur),^(18–22) which can be extremely debilitating. The literature is unclear as to whether FD lesions change over the life span of the affected individual. Some authors suggest that lesions become clinically quiescent with patient aging,^(19,23) whereas others support the concept that the disease does not change over time and that the FD lesions remain unabatedly active.⁽²⁴⁾ Insofar as hormonal changes that normally occur during puberty, pregnancy, and menopause affect normal bone, hormonal changes could be expected to affect the bones in patients with FD as well. The effect of puberty (precocious or normal) on FD is still unresolved. Kaplan et al.⁽²⁵⁾ reported worsening of FD during pregnancy. Despite the common association of hyperthyroidism⁽²⁶⁾ and phosphaturia⁽⁸⁾ with FD, there are no reports on how these two conditions affect the occurrence of fractures in this disease. We have previously shown, at the histopathological level, that hyperparathyroidism can have a direct and more pronounced effect on FD relative to normal bone.⁽¹²⁾

To better understand the incidence of extremity fractures in PFD and the effect of concomitant metabolic abnormalities, we performed a review of the medical records and studied a cohort of patients with PFD/MAS. We report on when the fractures occurred and the associations between fractures and metabolic abnormalities.

MATERIALS AND METHODS

Patients

Thirty-five patients were included in this retrospective study. All were enrolled over a 3-year period in a longitudinal, Institutional Review Board–approved study of the natural history of PFD/MAS at the National Institutes of Health. An additional 18 patients were screened but were excluded: 11 patients had disease confined to the craniofacial bones, 4 patients did not have complete surgical records available, and 3 patients did not have a diagnosis of FD. The group of four patients in whom records were not available consisted of two males and two females, 13–38 years of age: one had a diagnosis of PFD and three had a diagnosis of MAS. As such, they were demographically similar to the study group. The disease severity in the excluded four ranged from mild to severe. The diagnosis of FD was established on a combination of clinical, radiographic, and histological evaluations. The age range at the time of entry was 6–53 years (mean age, 24.5 years) at the time of enrollment. The retrospective review period ranged from 2 to 39 years (mean period, 14.2 years).

Surgical care was carried out at the institutions from which the patients were referred. The fracture histories were derived from medical records, including operative reports and a review of all available radiographs. The patients'

surgeons were contacted when clarification of treatment was necessary. All patient histories were corroborated with medical records. For each fracture, patient age, site of fracture, and treatment were noted, including any surgical interventions to correct a deformity that may have resulted in stabilization of the bone. Stress fractures or recurrent fractures, that is, fractures at the same site within 6 months, were excluded from the analysis. Four patients had been treated with a bisphosphonate drug at the time of the analysis. Two of the four had a history of precocious puberty, and the other two had phosphaturia in addition to a history of precocious puberty.

The presence or absence of endocrinopathy or phosphaturia was determined by a review of the medical records and an evaluation of pituitary, thyroid, and adrenal function and renal phosphorus handling. Female patients were considered to have precocious puberty if they had vaginal bleeding before the age of 8, and males if they developed secondary sexual characteristics before the age of 9. Hyperthyroidism was diagnosed if the serum thyroid-stimulating hormone (TSH) was suppressed below the normal range in the presence of an elevated serum triiodothyronine. The diagnosis of growth hormone (GH) excess was established when the serum GH concentration was >1.0 ng/dl at 120 minutes on a standard oral glucose tolerance test. The diagnosis of phosphaturia (renal phosphate wasting) was established if the tubular maximum of phosphate reabsorption relative to glomerular filtration rate (TmP/GFR) was below the age- and gender-specific normal range.⁽²⁷⁾ The single patient with Cushing's syndrome was diagnosed in the neonatal period by clinical assessment. The diagnosis of primary hyperparathyroidism was confirmed by resolution of disease after parathyroidectomy, when one patient underwent a parathyroidectomy for simultaneously elevated serum parathyroid hormone and ionized calcium levels. The phosphorus metabolism of this group has been previously described elsewhere.⁽⁸⁾

Fracture rate

To control for the differences in patient age and length of follow-up, the number of fractures were reported as fracture rate, that is, the mean number of fractures per patient per year within the indicated length of time. Time (in years) was divided into 5-year (or 15-year) intervals (Figs. 1–4). To establish the number of patients in each time interval, the number of patients evaluated in that interval was counted, and a patient whose age did not span the entire interval was reported as a fraction. This number was reported as the adjusted number of patients per age group.

Assays

Standard commercial assays for estradiol, thyroid function tests, serum growth hormone, insulin-like growth factor (IGF)-1, parathyroid hormone, urinary cortisol, ionized calcium, serum and urine phosphorus, and creatinine were performed.

Disease burden

Differences between groups could be the result of differences in the extent of skeletal disease (disease burden), and/or

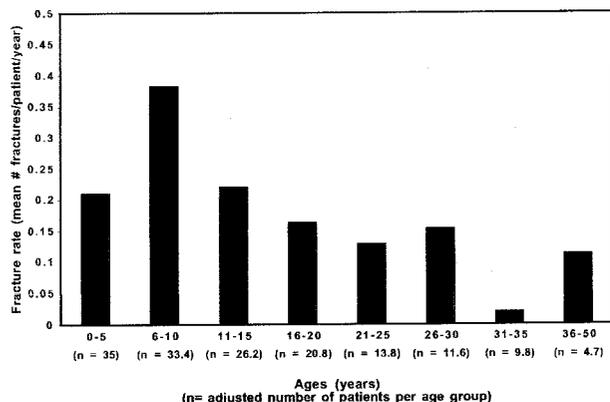


FIG. 1. Fracture rate for all fractures. The fracture rate for all fractures from all skeletal sites studied ($n = 172$) is shown according to age group. The adjusted number of patients in each age group is shown. If patient age only allowed inclusion for part of that period, the number of patients is reported as a fraction.

an intrinsic difference in the FD as a result of superimposed metabolic dysfunction. In attempt to assess these independent effects, the extent of skeletal involvement with FD was measured. Disease burden was measured using a standardized validated tool developed by the authors to quantify the amount of fibrous dysplasia, or disease burden. Briefly, patients underwent a standard ⁹⁹Tc-methylene diphosphonate (MDP) bone scan, and the percent of each segment of the skeleton that was involved with FD was estimated. The amount of the total skeleton that each segment represents was normalized to the percent of the total skeleton represented by that segment. These numbers were tallied to generate a “disease burden score.” The range of possible scores is from 0 (no FD) to 75 (100% of the skeleton involved with FD). Three patients did not have bone scans (one with PFD and two with PFD and precocious puberty) and were not included in the calculations of disease burden. The disease burden scores for the 32 patients were as follows: range, 0.6–75; mean, 40.1 ± 22.6 ; median, 40.0.

Statistical analysis

Statistical analyses were performed using SAS version 8.2 (SAS Institute, Cary, NC, USA). All numerically continuous parameters were summarized using median, mean, and SD. Groups were compared using the Wilcoxon rank-sum test. Correlations were examined using Spearman ρ correlation coefficients. p values less than 0.05 were considered statistically significant.

RESULTS

Patient characteristics

The 35 patient study cohort consisted of 22 females and 13 males. The median and mean ages at enrollment were 20 and 24.5 ± 13.1 years, respectively. Twenty-seven patients had PFD and concomitant metabolic dysfunction (MAS) with hyperfunctioning endocrinopathy and/or phosphaturia, and eight had PFD alone. Nineteen patients had precocious puberty, 9 patients had hyperthyroidism, 6 patients had GH excess, 1 patient each had Cushing syndrome and hyper-

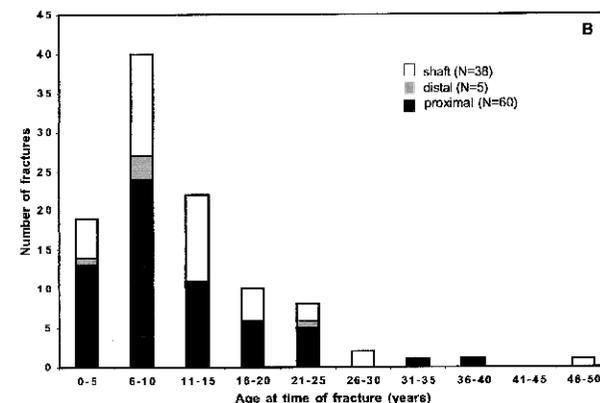
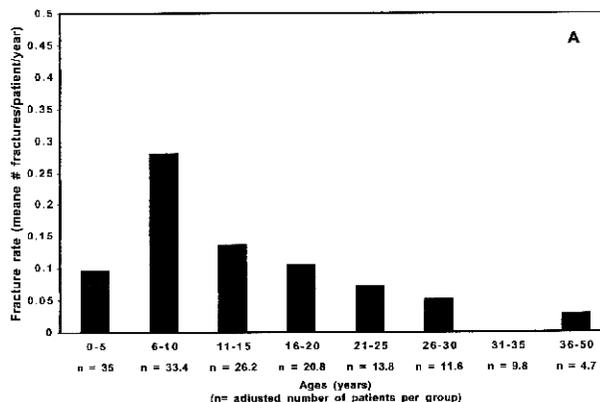


FIG. 2. Femur fractures, rate, and location. (A) Fracture rate in the femur and (B) the number of fractures by region of the femur are shown. One hundred three femur fractures were analyzed.

parathyroidism, and 12 patients had phosphaturia. Eleven of 27 patients (41%) had two or more endocrinopathies or phosphaturia. At the time of enrollment 17 of 19 patients (89%) had been treated for precocious puberty, and 7 of 9 (78%) had been treated for hyperthyroidism, whereas only 2 of 6 (33%) had been treated for growth hormone excess and 3 of 12 (25%) for phosphaturia. In 4 of 12 (33%) cases, the patients with phosphaturia had serum phosphorus levels in the low-normal range. Three of eight patients (38%) with frank hypophosphatemia were treated with phosphorus and calcitriol. The patient with Cushing syndrome had been surgically cured in the neonatal period and was on adrenal hormone replacement, whereas the patient with hyperparathyroidism had not been treated.

Fractures

Only fractures that occurred through FD lesions in the extremities were considered. A total of 172 fractures were identified and were subdivided by location: 103 femoral, 25 tibial, 33 humeral, and 11 forearm. Sixty of the femoral fractures were in the proximal third of the bone, 38 were in the midshaft region, and 5 were in the distal third. There were three stress fractures involving the femur and seven recurrent fractures involving the humerus, tibia, and forearm.

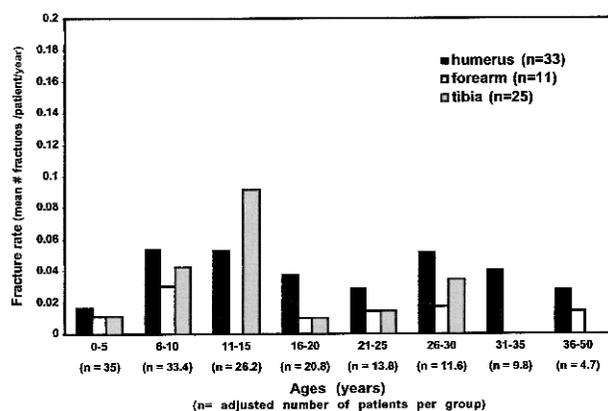


FIG. 3. Humerus, forearm, and tibia fracture rates. Fracture rates for the upper extremity and tibia are shown, with a lower rate than that seen in the femur, but with a pattern similar temporal pattern.

The fracture rate for all skeletal sites is shown in Fig. 1 and shows a peak fracture rate of 0.38 fractures per patient per year during ages 6–10. Similarly, the peak rate of femoral fractures (0.28 fractures per patient per year) occurred between the ages of 6 and 10 years and tapered off thereafter (Fig. 2A). Eighty-one (79%) of these fractures were treated with traction and/or casting, whereas the remaining 22 (21%) were treated surgically with the use of load-sharing or -shielding devices (including screw and side plate, intramedullary rod, or allograft strut). The pattern of the age at which fractures occurred in the different subregions of the femur (proximal, midshaft, or distal) was similar to that seen in the femur as a whole, namely a peak between 6 and 10 years and a decline in the number of fractures thereafter (Fig. 2B).

The rate of tibial fractures (14% of the total number and 24% of the lower extremity fractures) was significantly less than that of the femur (0.09 fractures per patient per year), peaked between the ages of 11–15, and tapered off with time, with no tibial fracture occurring after the age of 30 years (Fig. 3). Twenty-four of the 25 tibial fractures were treated with casting alone, and one patient was treated with an intramedullary rod.

Fractures involving the upper extremities (26% of the total number of fractures) occurred in a similar temporal pattern to those in the femur. That is, the peak rate of fractures occurred between the ages of 6 and 10 and declined thereafter, although the decline with age did not seem to be as marked as that in the femur (Fig. 3). Of the 33 humeral fractures, only 2 required surgery: 1 after the initial application of a cast had resulted in a nonunion, and another patient underwent osteotomy followed by fixation with Enders rods supported with cement to correct a deformity caused by multiple previous fractures that had occurred over a period of 8 years. All of the forearm fractures were managed nonsurgically, and all went on to heal uneventfully. Again, the peak period during which forearm fractures occurred was between 6 and 10 years of age, with a decreasing number of fractures thereafter.

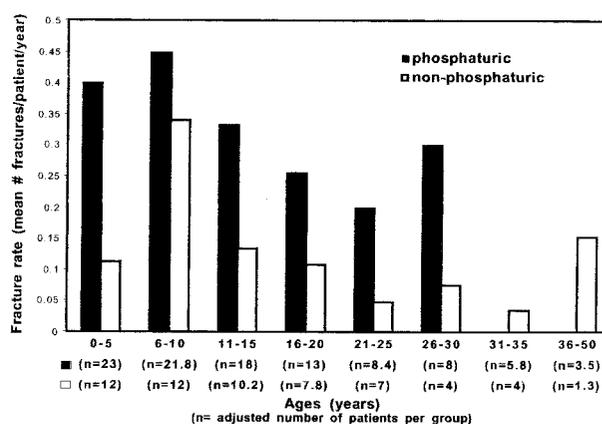


FIG. 4. Effect of phosphaturia on fracture rate. The fracture rate in the presence and absence of renal phosphate wasting is shown. The number of patients in each group for the age range is indicated. The ages of peak fracture incidence are the same, and the pattern of decline with age is similar.

Association with metabolic abnormalities

The age of first fracture, number of fractures, fracture rate, and disease burden were compared between patients with and without metabolic abnormalities (Table 1). Twenty-seven patients (77%) had one or more endocrinopathy and/or phosphaturia. While the group of patients with any endocrinopathy or phosphaturia had an earlier age of first fracture, a higher number of fractures, a higher rate of fractures, and higher disease burden, phosphaturia was the single metabolic derangement that had a statistically significant effect on all of these parameters. While the age interval in which the peak rate of fractures occurred (6–10 years) and the decline thereafter were similar in the groups of patients with and without phosphaturia, the group with phosphaturia had more fractures earlier, with a persistently higher fracture rate (Fig. 4).

The disease burden in the groups of patients with and without metabolic dysfunction was not statistically different (43.4 ± 22.4 versus 26.7 ± 21.9 ; $p > 0.05$; Table 1). However, patients with phosphaturia had significantly greater disease burden (50.8 ± 24.1 ; $p < 0.05$). Furthermore, in all patients, there were significant correlations between disease burden and age of first fracture (Spearman $\rho = -0.56$, $p = 0.001$) and disease burden and fracture density (Spearman $\rho = 0.60$, $p < 0.001$; Figs. 5A and 5B, respectively).

DISCUSSION

Fracture incidence in PFD has been poorly characterized, owing largely to its relative rarity and the broad spectrum of phenotypic heterogeneity seen in patients with this somatic mosaic disease. This study was undertaken to enhance our understanding of the incidence of fractures in PFD and the potential effect of concomitant metabolic abnormalities on fractures.

We found that there was a peak in the fracture rate between the ages of 6 and 10 years, with a decline thereaf-

TABLE 1. FRACTURES AND METABOLIC DYSFUNCTION

	Number of subjects (%)	Mean ± SD and median age of first fracture	Mean ± SD and median number of fractures	Mean ± SD and median fracture rate: age 0–20*	Mean ± SD and median fracture rate: lifetime	Mean ± SD and median disease burden†
Polyostotic fibrous dysplasia	8 (23)	16.6 ± 8.2 14.5	3.0 ± 4.9 1.0	0.08 ± 0.15 0.050	0.08 ± 0.09 0.040	26.7 ± 21.9 29.1
PFD with endocrinopathy and/or phosphaturia	27 (77)	6.9 ± 6.3** 5.0	5.6 ± 4.6§ 4.0	0.31 ± 0.25** 0.20	0.29 ± 0.25** 0.19	43.4 ± 22.4 46.0
Precocious puberty	19 (54)	7.6 ± 7.2 5.5	5.1 ± 4.2 4.0	0.27 ± 0.23 0.20	0.26 ± 0.22 0.18	45.1 ± 19.1 46.0
Hyperthyroidism	9 (26)	6.2 ± 4.0 5.0	6.4 ± 4.6 6.0	0.34 ± 0.24 0.30	0.32 ± 0.23 0.19	53.9 ± 16.6 56.5
Growth hormone excess	5 (14)	4.9 ± 1.3 5.0	7.0 ± 4.4 6.0	0.43 ± 0.36 0.40	0.44 ± 0.3 0.40	58.1 ± 16.1 58.3
Phosphaturia	12 (34)	5.1 ± 2.7§ 4.8	7.6 ± 5.1¶ 6.0	0.38 ± 0.26¶ 0.30	0.35 ± 0.26§ 0.26	50.8 ± 24.1§ 60.8

PFD, polyostotic fibrous dysplasia.

* Fracture rate, mean number of fractures/patient/year for the indicated period of time (0–20 years, or lifetime to date).

† Disease burden, relative amount of skeleton involved with FD (0–75 possible, see Materials and Methods Section).

‡ Eleven subjects had two or more endocrinopathies, or an endocrinopathy + phosphaturia.

§ *p* < 0.05; Wilcoxon rank-sum test, all *p* values reported represent the difference between the group indicated vs. all other groups without the indicated endocrinopathy and/or phosphaturia.

¶ *p* < 0.01.

** *p* < 0.005.

ter, most pronounced in the femur. Because only a small percentage of the total fractures was treated surgically or with load-sharing or -shielding devices (14%), which have been shown support the bone and protect against further fractures,⁽²⁸⁾ the decline in fracture number with age would seem to represent a true biological change in the lesional bone and not the effect of a surgical intervention. This conclusion is supported by the fact that the period of peak fracture rate in the upper extremities, which required far fewer surgeries, was similar to that seen in the lower extremities. Furthermore, the peak incidence of fractures seems to be an intrinsic property of the skeletal disease, because it was the same in patients with and without phosphaturia (Fig. 4).

There was a suggestion that there may be a second peak in the fracture rate after age 36 (Figs. 1, 2, and 4). This may represent the effect of normal aging (senile osteoporosis) superimposed on the already weakened bone. A similar observation has been made with osteogenesis imperfecta.⁽²⁹⁾ Continued observation of this group will determine if a similar pattern is seen in FD.

The age of first fracture, number of fractures, and fracture rate were aggravated by metabolic derangements, as demonstrated by the fact that patients with these conditions had first fractures at a younger age, more fractures, and a higher fracture rate. When this group was subdivided by type of endocrinopathy or phosphaturia, only phosphaturia had an independent effect on these parameters. Therefore, it seems that, of all the metabolic dysfunctions, phosphaturia had the most significant effect.

While not proven, it is thought that the stage at which mutation occurs during embryogenesis is related to the spatial distribution and extent of disease within a patient; that is, the earlier the mutation occurs the more widespread

the disease (MAS).⁽³⁰⁾ Mutations that occur later in development may result in only two, or even one, aspects of the MAS triad, and possibly less skeletal involvement. Therefore, it is possible that patients with phosphaturia fractured earlier and more often, simply because they have more skeletal disease. This was supported by the fact that the subgroup of patients with phosphaturia had a greater disease burden than any other subgroup. However, it may be that these patients fractured more often, not only because they had more skeletal disease, but that the quality of their bone was worse because of renal phosphate wasting inducing a relative hypophosphatemia. Our recent demonstration that the FD bone itself is the likely source of the phosphaturic factor fibroblast growth factor (FGF)-23⁽³¹⁾ makes it very difficult to separate disease burden effects from phosphaturia/hypophosphatemia effects, because FGF-23 levels and disease burden are correlated.

We have previously shown that FD bone is intrinsically osteomalacic to begin with,⁽³²⁾ and that phosphaturia worsens the degree of osteomalacia in lesional bone.⁽¹²⁾ It should be noted that another recent study failed to observe an exacerbation of the intrinsic osteomalacia of FD in the presence of phosphaturia and relative hypophosphatemia.⁽³³⁾ One explanation for this disparity may be the fact that the mean age of the group that did not show an exacerbation of the intrinsic osteomalacia⁽³³⁾ was significantly less (mean age, 10.0 years) than the group that did (mean age, 16.2 years),⁽¹²⁾ and that the accumulation of additional osteoid may require prolonged exposure to the relative hypophosphatemic state. It has been noted that renal phosphate wasting may not be present early in the course of FD but may require time for emergence.⁽³⁴⁾ Continued follow-up of this cohort will determine whether correction

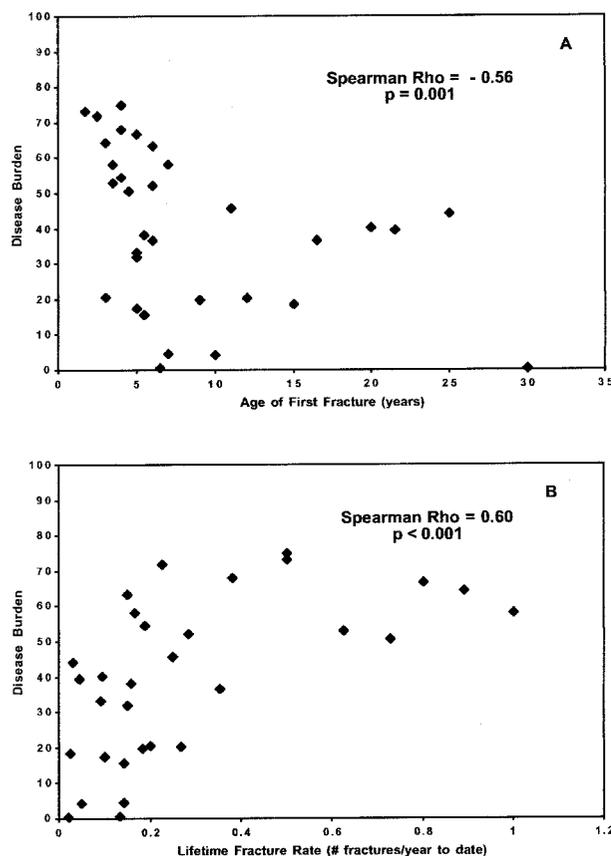


FIG. 5. Association between disease burden and age of first fracture and fracture rate. A significant association is demonstrated between (A) disease burden and the age of first fracture (Spearman $\rho = -0.56$, $p = 0.001$) and (B) lifetime fracture rate and disease burden (Spearman $\rho = 0.60$, $p < 0.001$).

of hypophosphatemia has a beneficial effect on the skeletal disease.

Orthopedic procedures that are focused on the prevention of fracture and improvement of deformity provide the mainstay of treatment in patients with PFD.^(35–37) Nonsurgical treatments of PFD, including the administration of calcitonin,⁽³⁸⁾ mithramycin,⁽³⁹⁾ and radiation,⁽⁴⁰⁾ were uniformly disappointing or frankly harmful. The initial report by Liens et al.⁽⁴¹⁾ on the use of bisphosphonates to treat FD heralded new hope for an effective medical treatment. These findings and those of subsequent reports from additional uncontrolled trials suggest that bisphosphonates decrease pain, improve the radiographic appearance of lesions, and decrease the fracture rate,^(42–44) and it has also been suggested that bisphosphonates in combination with surgical instrumentation may have added benefit.⁽⁴⁵⁾ However, the findings of these studies may need to be reinterpreted in light of the data on the age-related incidence of disease presented here. An awareness of the tendency for the fracture rate to decrease after the age of 10 years is essential for greater accuracy in prognostication, clinical management, and the design and interpretation of therapeutic interventions. It remains to be seen if these findings extend to other skeletal sites such as the skull and spine, which were not studied.

Based on the data retrieved from our study population, we were able to conclude that the peak fracture incidence in PFD occurs between the ages of 6 and 10 years, with a reduction thereafter. We also conclude that phosphaturia, which is commonly associated with PFD, is likely to contribute to the propensity of lesional bone to fracture. These data have important implications, not only in terms of patient care, but also point to the need for future studies to define the natural history of the disease and the impact of metabolic dysfunction on it. Furthermore, these findings should be considered in the design and interpretation of treatment studies of PFD.

ACKNOWLEDGMENTS

We thank the study participants and their families, as well as the research nurses (Janet Jones and Susan Booher) and the Inter-institute Training Program Endocrine Fellows of the National Institutes of Health for their care of the patients. This study was funded by the National Institutes of Health, Intramural Funding to the National Institute of Dental and Craniofacial Research, and Telethon Fondazione Onlus Grant E1029 (PB).

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Received in original form May 30, 2003; in revised form July 30, 2003; accepted December 19, 2003.